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Research Recommendations for Selected IARC-Classified Agents: Impact and Lessons Learned

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Background: The International Agency for Research on Cancer (IARC) Monographs program assembles expert working groups who publish a critical review and evaluation of data on agents of interest. These comprehensive reviews provide a unique opportunity to identify research needs to address classification uncertainties. A multidisciplinary expert review and workshop held in 2009 identified research gaps and needs for 20 priority occupational chemicals, metals, dusts, and physical agents, with the goal of stimulating advances in epidemiological studies of cancer and carcinogen mechanisms. Overarching issues were also described.

Objectives: In this commentary we review the current status of the evidence for the 20 priority agents identified in 2009. We examine whether identified Research Recommendations for each agent were addressed and their potential impact on resolving classification uncertainties.

Methods: We reviewed the IARC classifications of each of the 20 priority agents and identified major new epidemiological and human mechanistic studies published since the last evaluation. Information sources were either the published Monograph for agents that have been reevaluated or, for agents not yet reevaluated, Advisory Group reports and literature searches. Findings are described in view of recent methodological developments in Monographs evidence evaluation processes.

Discussion: The majority of the 20 priority agents were reevaluated by IARC since 2009. The overall carcinogen classifications of 9 agents advanced, and new cancer sites with either "sufficient" or "limited" evidence of carcinogenicity were also identified for 9 agents. Examination of published findings revealed whether evidence gaps and Research Recommendations have been addressed and highlighted remaining uncertainties. During the past decade, new research addressed a range of the 2009 recommendations and supported updated classifications for priority agents. This supports future efforts to systematically apply findings of Monograph reviews to identify research gaps and priorities relevant to evaluation criteria established in the updated IARC Monograph Preamble. https://doi.org/10.1289/EHP12547

Introduction

The International Agency for Research on Cancer (IARC) Monographs program identifies the carcinogenic hazard to humans posed by a range of chemicals, physical and biological agents, complex mixtures, personal habits, and workplace exposures. Since 1971, 127 agents have been classified as "carcinogenic to humans" (Group 1), 418 as "probably" (Group 2A) or "possibly" (Group 2B) carcinogenic, and 500 as "not classifiable" as to their carcinogenicity to humans (Group 3).[1] In the Monographs program, IARC assembles international expert working groups (WGs) who publish a systematic review and evaluation of existing data on each agent of interest and reveal research gaps through critical assessment of the body of evidence and general remarks regarding classification uncertainties.

The number of Group 1 agents with occupational relevance increased from 28 (of 89 total Group 1 agents) identified through 2003[2] to 47 (of 119 Group 1 agents) in 2017.[3] There were also an additional 12 more broadly defined occupations, industries or processes classified in Group 1 with "sufficient" evidence in humans.[3] However, there remains inadequate epidemiological evidence for many workplace exposures of concern.

Studies of cancer in workers have been instrumental in identifying causes of cancer in humans, often with direct relevance to the general population and public health.[3] Studies of cancer in workers are often facilitated by well-defined groups of exposed workers, who may be exposed to high levels of the agent under study.[3]

Occupational exposure to 14 Group 1 agents was estimated to account for 349,000 (95% uncertainty interval: 269,000–427,000) cancer deaths worldwide in the year 2016.[4] Estimates of the work-related burden of disease for the years 2000–2016 have also been provided.[5] There is a need for ongoing research on occupational causes of cancer to address a lack of epidemiological data, including of quantitative exposure and exposure–response data, also in low- and middle-income countries.[3]

To identify research gaps and needs for 20 priority occupational chemicals, metals, dusts, and physical agents, a multidisciplinary expert workshop was previously held in June–July 2009 to discuss Research Recommendations for agents with evidence of widespread human exposure but for which the evidence of carcinogenicity was less than conclusive.[6,7] Most agents were classified at that time in either Group 2A or 2B with "sufficient" evidence of carcinogenicity in animals but "limited" or "inadequate" evidence in humans. The ultimate aim of the workshop was to identify uncertainties in the classification of these agents so as to stimulate more definitive studies. Specific research gaps and needs were outlined for each of the 20 agents largely regarding new epidemiological studies or human studies of cancer mechanisms. In addition, overarching issues related to multiple carcinogenic pathways, exposure assessment, and study design were described.

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Recent methodological advances in Monographs evaluation include an update/amendment of the Preamble describing procedures for evidence synthesis and cancer hazard identification.[8] Advances include strengthening systematic review methodologies, improved harmonization of evaluation criteria, and integration of evidence from different streams. The updated Preamble also emphasizes evaluation of exposure assessment quality in key studies and enhanced consideration of mechanistic evidence using key characteristics (KCs) of carcinogens.[9,10] The use of flexible and tailored approaches in the assessment of study quality was described.

The KCs, which are the chemical and biological properties associated with established (Group 1) human carcinogens, support these advancements by providing the basis for an unbiased approach to systematically identifying, organizing, and summarizing mechanistic information.[9,10] The KCs describe the actions of carcinogens and are distinct from the hallmarks of cancer, which are the properties of cancer cells.[11] When the evidence of cancer in humans is less than sufficient, strong evidence of the KCs can alone provide evidence of carcinogenicity or strengthen conclusions based on studies of cancer in humans or in experimental animals. For instance, strong evidence of KCs from studies of exposed humans (e.g., workers) can support classification in Group 1 when evidence of cancer in experimental animals is "sufficient," whereas strong evidence of KCs in experimental systems can support classification in Group 2A when evidence of cancer in humans is "limited." Because noncarcinogens can induce some KCs (e.g., protein adducts, oxidative stress, chronic inflammation), mechanistic conclusions based on these and other KCs can be strengthened when there is additional supporting evidence, such as suppression of tumor development when key mechanistic processes are suppressed or when they are found in combination with other KCs. The KCs were first formally applied in 2015 in Monographs Volume 112[12] and have served as a model for other toxicity end points, including male and female reproductive toxicants, endocrine disrupting chemicals, hepatotoxicants, and cardiotoxicants.[13,14]

The objective of this commentary is to provide a review of the current status of the evidence for the 20 previously identified priority occupational agents.[6,7] Here, we detail whether the previously identified research gaps and needs for each agent were addressed, what the findings were, and, for agents that have already been reevaluated, the resultant impact on resolving classification uncertainties. Lessons learned from research and evaluation of the 20 agents are detailed with a view to inform future occupational epidemiology and human mechanistic studies relevant to identification of carcinogenic hazards to humans.

Methods

We grouped the 20 agents into *a*) those that have been reevaluated by IARC WGs since the 2009 workshop, and *b*) those that have not been reevaluated (Tables 1–3; Figure S1). For agents that have been reevaluated by IARC WGs, we reviewed the updated Monographs to identify major new epidemiological and human mechanistic evidence published since the Research Recommendations workshop. We evaluated whether the studies that were recommended were achieved and to what extent they were informative in the reevaluation. We further categorized the agents into *a*) those where the overall classification was updated (Table 1), and *b*) those where the overall classification was not updated (Table 2).

For agents that have not been reevaluated since the 2009 workshop (Table 3), we relied mainly on the reports of the 2014 and 2019 Advisory Groups to Recommend Priorities for the IARC Monographs[15–18] to identify major new epidemiological and human mechanistic studies. The 2019 Advisory Group reviewed >170 nominated agents and provided recommendations as to the priority level and readiness for (re-)evaluation of each agent based on evidence of human exposure and carcinogenicity from the published literature and >60 databases.[16,18] A complementary database fusion and text mining exercise was also conducted to facilitate agent grouping and analysis of data gaps.[19] For two agents [propylene oxide and refractory ceramic fibers (RCFs)] that were not considered by either the 2014 or 2019 Advisory Groups we performed systematic literature searches to identify major new published studies for these agents (see https://hawcproject.iarc.who.int/assessment/705/ for propylene oxide and https://hawcproject.iarc.who.int/assessment/701/ for RCFs).

For all agents, including those that were reevaluated by IARC WGs close in time following the 2009 workshop for which there would be insufficient time to implement the Research Recommendations, we also reviewed the priority level for reevaluation of the 2014 and 2019 Advisory Groups and progress in the status of the available evidence for each agent as an additional indicator as to whether the identified recommendations were achieved. For most agents, the evidence from studies of experimental animals was already "sufficient" prior to the 2009 workshop (with the exception of styrene and welding fumes) and is not detailed here. A more detailed definition of the agents and exposure circumstances is provided elsewhere.[6,7,15,18] Below we provide an overview of the status of the available evidence for each agent in relation to the Research Recommendations.

Discussion

Agents That Were Reevaluated and for Which the Classification Was Updated

Table 1 and Figure S1 present a summary of 10 agents that were reevaluated or partially reevaluated (acetaldehyde associated with consumption of alcoholic beverages, metallic cobalt without tungsten carbide) by IARC WGs since the 2009 Research Recommendations workshop where the overall classification was updated (or where a new cancer site was identified for a Group 1 agent, formaldehyde).[20–29] For 7 of the agents, advances in human epidemiological evidence supported the updated classification [acetaldehyde associated with consumption of alcoholic beverages,[20] diesel engine exhaust (DEE),[23] formaldehyde,[21] methylene chloride (dichloromethane; DCM),[26] polychlorinated biphenyls (PCBs),[25] trichloroethylene (TCE),[24] welding fumes[27]]. For 3 agents (di-2-ethylhexyl phthalate,[22] metallic cobalt without tungsten carbide,[29] styrene[28]), the updated classification was supported by mechanistic data.

Acetaldehyde. Acetaldehyde was evaluated in 1998 and classified in Group 2B.[30] Findings from a small number of case–control studies showed an increased risk of alcohol-related cancers among those with genetic polymorphisms related with higher internal doses of acetaldehyde following heavy alcohol consumption, although evidence in humans was considered "inadequate."

Research Recommendations included new epidemiological studies to examine acetaldehyde exposures from all sources (including occupational exposures in the flavoring industry) and cancer with robust exposure assessment and genotyping to identify alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) (and other enzyme) deficiencies.[6,7] Use of acetaldehyde-derived DNA adducts as exposure biomarkers was suggested to minimize exposure misclassification (e.g., in nested case–control studies using specimens collected at enrollment).

In 2009, acetaldehyde associated with consumption of alcoholic beverages was reevaluated and classified in Group 1 based on "sufficient" evidence of cancer in humans for cancers of the esophagus and upper aerodigestive tract.[20] Humans deficient in the oxidation of acetaldehyde to acetate had a substantially increased risk of alcohol-related cancers. Heterozygous carriers

Table 1. Ten agents that were reevaluated or partially reevaluated since the 2009 Research Recommendations expert workshop where the overall classification was advanced (or a new cancer site was identified for an existing Group 1 agent) (alphabetical).

	Previous evaluation						Subsequent reevaluation							
Agent	Year of meeting (vol.)	Human	Animal	Overall evaluation	Cancer sites	Research Recommendations from 2009 expert workshop[6,7]	Year of reevaluation meeting (vol.)	Human	Animal	Mechanism/ KCs	Overall reevaluation	Cancer sites	Rationale	Informative studies in humans	2019 Advisory Group priority level for reevaluation[15,16]
Acetaldehyde	1998 (71)	I	S	2B	—	Exposure characterization in occupational settings, new epidemiological studies considering all exposure sources, and using genotyping, exposure biomarkers	Acetaldehyde associated with consumption of alcoholic beverages 2009 (100E)	S	S	Is genotoxic	1	Esophagus (S), upper aerodigestive tract combined (S)	Based on "sufficient" evidence of cancer in humans. Alcohol consumption and ethanol Group 1	Epidemiological studies of humans deficient in oxidation of acetaldehyde to acetate	High priority (new mechanistic evidence)
Di-2-ethylhexyl phthalate (DEHP)	2000 (77)	I	S	3	—	Improved exposure characterization including in established PVC-processing worker cohorts using specific biomarkers, studies in mouse models of human PPARα	2011 (101)	I	S	Multiple mechanisms of action	2B	—	Based on "sufficient" evidence of cancer in experimental animals	—	Not considered
Diesel engine exhaust	1988 (46)	L	S	2A	Lung (L), urinary bladder (L)	Completion of studies in U.S. nonmetal miners and in truck driver cohorts; mechanisms including of biomarkers of inflammation, genotoxicity, other relevant early effects, most relevant components	2012 (105)	S	S	Is genotoxic, induces oxidative stress, and induces chronic inflammation	1	Lung (S), urinary bladder (L)	Based on "sufficient" evidence of cancer in humans	Epidemiological studies in nonmetal miners, railroad workers, and in trucking industry, with well-characterized exposure	Not considered
Formaldehyde	2004 (88)	S	S	1	Nasopharynx (S), leukemia (L), sinonasal (L)	Follow-up of occupational cohorts for incident cancers and with appropriate lymphohematopoietic cancer classification, studies of genotoxic and hematologic effects with biological markers of internal dose, studies of mechanisms of myeloid leukemia	2009 (100F)	S	S	Is genotoxic	1	Nasopharynx (S), leukemia (S), sinonasal (L)	Based on "sufficient" evidence of cancer in humans	Nested case–control study of embalming workers with lifetime exposure metrics, mechanistic study of cultured myeloid progenitor cells from peripheral blood of exposed workers and controls of leukemia-specific chromosomal changes	Not considered (other aldehydes or relevant exposures were considered)
Metallic cobalt (without tungsten carbide)	2003 (86)	I	S	2B	—	See Metallic cobalt (with tungsten carbide) (Table 3)	2022 (131)	I	S	Cobalt metal is genotoxic, induces oxidative stress; soluble cobalt (II) compounds: genotoxic, and induce cell proliferation	2A	—	Based on "sufficient" evidence of cancer in experimental animals and "strong" mechanistic evidence in primary human cells	Mechanistic evidence in human primary cells	High priority (cobalt and cobalt compounds, new mechanistic evidence)
Methylene chloride [dichloromethane (DCM)]	1998 (71)	I	S	2B	—	New large occupational cohorts including female workers and robust exposure assessment, cancer of the brain, breast, and lymphohematopoietic system, biological (urinary) markers, metabolites and mechanisms	2014 (110)	L	S	Metabolically activated to an electrophile, is genotoxic	2A	Biliary tract (L), NHL (L)	Based on "sufficient" evidence of cancer in experimental animals and "limited" evidence of cancer in humans	Supported by strong evidence that metabolism via GSTT1 leads to formation of reactive metabolites, GSTT1 activity associated with genotoxicity *in vitro* and *in vivo*, GSTT1-mediated metabolism occurs in humans	Low priority

Table 1. (*Continued.*)

	Previous evaluation						Subsequent reevaluation							
Agent	Year of meeting (vol.)	Human	Animal	Overall evaluation	Cancer sites	Research Recommendations from 2009 expert workshop[6,7]	Year of reevaluation meeting (vol.)	Human	Animal	Mechanism/ KCs	Overall reevaluation	Cancer sites	Rationale	Informative studies in humans	2019 Advisory Group priority level for reevaluation[15,16]
Polychlorinated biphenyls (PCBs)	1987 (suppl 7)	L	S	2A	Hepatobiliary cancer (L)	Occupational cohorts of highly exposed workers including in existing U.S. and new international cohorts and analysis of blood PCB levels, studies of mechanisms (ROS, oxidative stress and DNA damage, DNA adducts, cell proliferation)	2013 (107)	S	S	Alters receptor-mediated effects, also electrophilicity, genotoxicity, oxidative stress, cell proliferation, immune suppression, and inflammation	1	Malignant melanoma (S), NHL (L), breast (L)	Based on "sufficient" evidence of cancer in humans. An additional Group-1 evaluation of dioxin-like PCBs was based on strong evidence of a receptor-mediated mechanism similar to TCDD. Carcinogenicity of PCBs cannot be attributed solely to that of dioxin-like PCBs	Studies of workers in industries where PCBs were used, including cohorts of workers in manufacture of capacitors and transformers, and in electric power and equipment maintenance, population-based case–control studies with serum PCB levels	No evaluation (dietary exposure, encompassed in previous evaluation)
Styrene	2002 (82)	L	L	2B	Lymphatic and hematopoietic (L)	Occupational cohorts of cancer incidence, updating existing studies with appropriate lymphohematopoietic cancer classification, pooled studies of chromosomal aberrations and other genotoxic effects, metabolites and mechanisms. See also Styrene-7,8-oxide (Table 2)	2018 (121)	L	S	Metabolically activated to an electrophile, is genotoxic, alters cell proliferation, modulates receptor-mediated effects	2A	Lymphohematopoietic (L)	Based on "sufficient" evidence of cancer in experimental animals and "limited" evidence in humans	Large occupational cohorts in reinforced plastics industry with high exposure levels	Medium priority (styrene–acrylonitrile trimer)
Trichloroethylene (TCE)	1995 (63)	L	S	2A	Liver and biliary tract (L), NHL (L)	Meta-analyses, new occupational cohorts without multiple solvent exposures, mechanisms and metabolites for specific sites, cell-signaling and epigenetic changes, genetic polymorphisms	2012 (106)	S	S	Metabolically activated to an electrophile, is genotoxic, is immunosuppressive	1	Kidney (S), liver (L), NHL (L)	Based on "sufficient" evidence of cancer in humans	Occupational case–control studies in different geographic areas, *GSTT1* polymorphism, cohort studies of aircraft and aerospace workers, meta-analysis	No evaluation
Welding fumes	1989 (49)	L	I	2B	Lung (L)	New and updated cohorts with detailed exposure assessment and smoking data, experimental studies of different welding fumes components and epigenetic mechanisms, gene expression pathways, functional level changes	2017 (118)	S	L	Induces chronic inflammation and is immunosuppressive	1	Lung (S), kidney (L)	Based on "sufficient" evidence of cancer in humans	Numerous case–control studies and occupational or population-based cohort studies, detailed exposure information, evaluation of potential confounding (asbestos, smoking)	Not considered

Note: Priority level for reevaluation of the 2019 Advisory Group was assigned based on evidence of human exposure and the extent and potential impact of the available evidence for evaluating carcinogenicity (i.e., in humans, experimental animals, and mechanisms) to support a new or updated evaluation, also including during integration across evidence streams. See also https://monographs.iarc.who.int/monographs-available/. —, Not applicable; GSTT1, glutathione *S*-transferase theta 1; I, inadequate; KC, key characteristic; L, limited; NHL, non-Hodgkin lymphoma; PPARα, peroxisome proliferator-activated receptor alpha; PVC, polyvinyl chloride; ROS, reactive oxygen species; S, sufficient; suppl, supplement; TCDD, 2,3,7,8-tetrachlordibenzo-para-dioxin; vol, volume.

Table 2. Four agents that were reevaluated or partially reevaluated since the 2009 Research Recommendations expert workshop where the overall classification did not advance (alphabetical).

	Previous evaluation						Subsequent reevaluation							
Agent	Year of meeting (vol.)	Human	Animal	Overall evaluation	Cancer sites	Research Recommendations from 2009 expert workshop[6,7]	Year of reevaluation meeting (vol.)	Human	Animal	Mechanism/ KCs	Overall reevaluation	Cancer sites	Rationale	Informative studies in humans	2019 Advisory Group priority level for reevaluation[15,16]
Indium phosphide and other indium compounds	2003 (86)	I	S	2A (indium phosphide)	—	New epidemiological studies in secondary refining, studies of pulmonary effects, exposure and biomarker studies of genetic damage, mechanisms	2017 (118)	I	S	Induces chronic inflammation	2B (indium tin oxide)	—	Based on "sufficient" evidence of cancer in experimental animals	—	Not considered
Shift work	2007 (98)	L	S	2A	Female breast (L)	Studies using improved exposure definitions/metrics, markers of circadian disruption in non–day shift workers, improved control descriptions, circadian genes, other cancers, susceptibility to other chemical exposures	Night shift work 2019 (124)	L	S	Is immunosuppressive, induces chronic inflammation, alters cell proliferation	2A	Breast (L), prostate (L), colon (L), rectum (L)	Based on "sufficient" evidence of cancer in experimental animals, "limited" evidence of cancer in humans, and "strong" mechanistic evidence in experimental systems	Large-scale case–control studies with high-quality exposure assessment	Not considered
Styrene-7,8-oxide	1994 (60)	I	S	2A	—	See Styrene (Table 1)	2018 (121)	I	S	Is electrophilic, is genotoxic, alters cell proliferation	2A	—	Based on "sufficient" evidence of cancer in experimental animals and "strong" mechanistic evidence in human systems	Strong evidence in human systems, mechanism can also operate in humans	Medium priority (styrene–acrylonitrile trimer)
Tetrachloroethylene (perc)	1995 (63)	L	S	2A	Esophageal (L), NHL (L), cervical (L)	New studies in dry-cleaning workers using exhaled-breath specimens, pooling of U.S. cohorts, new cohorts outside of the United States and Europe, mechanisms including identification of sensitive subpopulations and target organs	2012 (106)	L	S	Multiple mechanisms of action	2A	Urinary bladder (L)	Based on "sufficient" evidence of cancer in experimental animals	Cohort studies of dry-cleaning workers, case–control studies of Perc exposure or of work in dry-cleaning shops	High priority (human cancer evidence)

Note: Priority level for reevaluation of the 2019 Advisory Group was assigned based on evidence of human exposure and the extent and potential impact of the available evidence for evaluating carcinogenicity (i.e., in humans, experimental animals, and mechanisms) to support a new or updated evaluation, also including during integration across evidence streams. See also https://monographs.iarc.who.int/monographs-available/. —, Not applicable; I, inadequate; KC, key characteristic; L, limited; NHL, non-Hodgkin lymphoma; S, sufficient; vol, volume.

Table 3. Eight agents or partial agents that have not been reevaluated since the 2009 Research Recommendations expert workshop (alphabetical).

Agent	Previous evaluation					Research Recommendations from 2009 expert workshop[6,7]	2019 Advisory Group priority level for reevaluation[15,16]
	Year of previous meeting (vol.)	Human	Animal	Overall evaluation	Cancer sites		
Atrazine	1998 (73)	I	S	3	—	Updated follow-up of agricultural cohorts, analysis of biomarkers, studies of exposed women, relevance of mechanism in rats for humans, pathways disrupted, immune function and aromatase	Medium priority
Carbon black	2006 (93)	I	S	2B	—	Updated larger occupational cohorts with data on particle size and surface area, study of late-stage carcinogen, biomarkers of oxidative stress	Low priority
Chloroform (trichloromethane)	1998 (73)	I	S	2B	—	Case–control studies with information on route of exposure and detailed DBP assessment, pooled studies, studies of exposed occupations, updated follow-up of cohorts of medical personnel	High priority (haloacetic acids and other DBPs—human cancer, bioassay, mechanistic evidence)
Lead and lead compounds	2004 (87)	L	S	2A	Stomach (L)	New and updated occupational cohorts with well-documented exposure, background rates, and internal dose–response analyses, correlations of blood with bone lead, *H. pylori* infection and exposure, genetic susceptibility factors, mechanisms	High priority (mechanistic evidence)
Metallic cobalt (with tungsten carbide)	2003 (86)	L	S	2A	Lung (L)	New and updated occupational cohorts of hardmetal production workers, biomarkers of exposure and early cellular effects, genetic polymorphisms of cellular protective systems, toxicity of nanoparticles	No evaluation
Propylene oxide	1994 (60)	I	S	2B	—	New and updated occupational cohorts, including women (potential mammary carcinogen), exposure-selective cross-sectional studies of hemoglobin and DNA adducts and cytogenetic effects	Not considered
Refractory ceramic fibers (RCFs)	2001 (81)	I	S	2B	—	New and updated occupational cohorts, including of cancer incidence, animal studies of combined effects with granular low biosoluble particles, impact of fiber length, sensitive rat inhalation model	Not considered
Titanium dioxide (TiO_2)	2006 (93)	I	S	2B	—	Epidemiological studies with well-characterized exposure, including of workers producing or using nanoscale TiO_2 (cosmetic industry), multiple routes and general population exposure, TiO_2 in tissues, mechanisms of particle-induced inflammation and lung cancer, quantitative comparison oxidative stress in workers and rodents	Medium priority (nanomaterials, including TiO_2)

Note: Priority level for reevaluation of the 2019 Advisory Group was assigned based on evidence of human exposure and the extent and potential impact of the available evidence for evaluating carcinogenicity (i.e., in humans, experimental animals, and mechanisms) to support a new or updated evaluation, also including during integration across evidence streams. See also https://monographs.iarc.who.int/monographs-available/. —, Not applicable; DBP, disinfection by-product; *H. pylori*, *Helicobacter pylori*; I, inadequate; L, limited; S, sufficient; vol, volume.

of the *ALDH2* genotype, prevalent in East-Asian populations, had reduced enzyme activity, accumulated acetaldehyde, and had higher risk of alcohol-related cancers.[31] Acetaldehyde in other exposure settings was not reevaluated.

The 2019 Advisory Group recommended acetaldehyde be reevaluated with high priority owing to new mechanistic evidence.[16,18] There is substantial evidence that acetaldehyde forms persistent DNA adducts after direct or indirect exposure through alcohol consumption. Increases in acetaldehyde-specific DNA adducts were reported in oral cells from volunteers exposed to alcohol,[32] in rats exposed to acetaldehyde for 50 d,[33] and in rhesus monkeys exposed to alcohol drinking over their lifetime.[34] There is evidence relevant to several KCs that acetaldehyde is electrophilic, genotoxic, alters DNA repair, induces epigenetic alterations, and induces oxidative stress.[35] There is also new evidence of acetaldehyde associated with alcoholic beverage consumption and cancer of other digestive organs in recent genetic epidemiological studies. Acetaldehyde may be part of a mechanistic class that includes Group 1 formaldehyde (below).

Di-2-ethylhexyl phthalate. In 2000, di-2-ethylhexyl phthalate (DEHP) was classified in Group 3.[36] Although DEHP increased the incidence of hepatocellular tumors in rats and mice, the mechanism

[induction of peroxisome proliferator-activated receptor-α (PPARα)] was judged not relevant to humans. There was one small mortality study of workers in a DEHP production plant, with no evidence of excess cancer mortality, and the human evidence was "inadequate." There were no available studies of long-term dialysis patients who may be exposed to DEHP due to leaching from surgical tubing.

Research Recommendations included better characterization of DEHP in established polyvinyl chloride (PVC) processing industry cohorts, including with specific biomarkers [mono-2-ethylhexyl phthalate and mono(2-ethyl-5-carboxypentyl) phthalate], as well as additional studies in mouse models of human PPARα.[6,7] Difficulties in conducting informative epidemiological studies were noted and were due to challenges in identifying highly exposed workers.

DEHP was reevaluated in 2011 and classified in Group 2B based on "sufficient" evidence in experimental animals.[22] New mechanistic data suggested that the human relevance of tumors in the rodent liver could not be ruled out. Subacute, subchronic, and chronic studies in PPARα-null mice, as well as in transgenic mouse lines, supported multiple molecular signals and pathways in DEHP carcinogenesis rather than a single molecular event.

Evidence in humans remained "inadequate." A case–control study published following the Research Recommendations workshop evaluated urinary levels of nine phthalate metabolites (obtained after diagnosis in cases but before treatment) and breast cancer risk.[37] There were positive associations with four metabolites, one of which was statistically significant for a metabolite [mono(2-ethyl-5-carboxypentyl) phthalate] with a dose–response trend. Results from studies of workers potentially exposed to DEHP, including PVC workers, remained inconsistent and were based on small numbers.

Diesel engine exhaust (DEE). DEE was classified in Group 2A in 1988.[38] There was "limited" evidence for cancers of the lung and urinary bladder in humans. Although positive associations in previous epidemiological studies were observed, there were limitations in exposure assessment and concerns regarding potential confounding by cigarette smoking and other occupational exposures.

Research Recommendations included completion of lung cancer studies in U.S. nonmetal miners and transport workers with estimated quantitative historical exposure data.[6,7] DEE was reevaluated in 2012 and classified in Group 1, with "sufficient" evidence for lung cancer in humans and "limited" evidence for cancer of the urinary bladder.[23] There were consistent positive associations observed across a range of studies and occupational settings for lung cancer; many of which controlled for cigarette smoking. The most informative studies were those that were recommended based in cohorts of nonmetal miners, railroad workers, and workers in the trucking industry, with well-characterized exposures.

In U.S. nonmetal miners, with a wide range of DEE exposures, there were positive trends in lung cancer risk, with increasing DEE using estimated elemental carbon as a proxy of exposure.[39] Mines were selected to minimize exposure to other potential confounders, such as silica, radon, and asbestos; a nested case–control study adjusted for cigarette smoking, previous respiratory disease, and history of high-risk jobs.[40] There was no clear association with urinary bladder cancer.

In U.S. transport workers, with light-to-moderate exposures, there were positive trends for lung cancer risk with increasing duration of employment among drivers, both pick-up and delivery, and dock workers, which remained with indirect adjustment for cigarette smoking.[41] In analysis using current elemental carbon measurements for historical exposure reconstruction, there were positive trends with cumulative (but not average) exposure.[42] There were also positive findings for lung cancer in U.S. railroad workers,[43,44] as well as in a pooled analysis of 11 case–control studies.[45]

Research Recommendations also included cross-sectional studies of biomarkers of inflammation, genotoxicity, and other early biological effects, as well as identification of relevant DEE components.[6,7] The reevaluation noted that there was "strong" mechanistic evidence that whole DEE, including many of its components, is genotoxic, induces oxidative stress, and causes chronic inflammation. Other carcinogenic agents present in DEE alter cell proliferation, cell death, and nutrient supply and thereby contribute to carcinogenicity.

Formaldehyde. Formaldehyde was evaluated in 2004 and classified in Group 1.[46] There was "sufficient" evidence for nasopharyngeal cancer in humans. The evidence was "limited" for both leukemia (owing to limited or inconsistent findings in cohorts of industrial workers) and sinonasal cancer.

Research Recommendations included additional follow-up of existing occupational cohorts, analysis of incident cancers, appropriate classification of lymphohematopoietic cancers, studies of genotoxic and hematologic effects, including markers of internal dose, and mechanistic studies for inhaled formaldehyde, including of exposure to circulating blood or stem cells in the nose and pathways to bone marrow and lymphatic tissue.[6,7]

Formaldehyde was reevaluated in 2009[21] with "sufficient" evidence for both nasopharyngeal cancer and leukemia in humans. There were few new studies on nasopharyngeal cancer, although there were reevaluations of previous studies and meta-analyses. For leukemia there was an update of the U.S. cohort and a nested case–control study of professionals in the funeral industry and meta-analyses. There was evidence of elevated mortality due to lymphohematopoietic malignancies of nonlymphoid origin in the nested case–control study, with lifetime embalming exposure metrics addressing limitations in exposure assessment in previous proportionate mortality studies.[47] There were also positive findings in an updated follow-up of a U.S. cohort of industrial workers, particularly for myeloid leukemia and peak exposure.[48] A meta-analysis reported positive associations of formaldehyde and leukemia risk overall and of myeloid leukemia specifically.[49] Evidence for sinonasal cancer remained "limited" owing to discordant findings in case–control and cohort studies, as well as concerns regarding potential residual confounding by wood dust exposure.

Formaldehyde is genotoxic in nasal tissues in humans.[21] Exposed workers had numerical chromosomal aberrations in myeloid progenitor cells consistent with myeloid leukemia and hematological changes in peripheral blood suggesting effects on bone marrow.[50] Formaldehyde alters cell proliferation, cell death, and nutrient supply. Different genotoxic mechanisms of induction of hematological malignancies in humans were described; further research was suggested to clarify their relevance.

Metallic cobalt (with or without tungsten carbide). Metallic cobalt was evaluated in 2003.[51] A high percentage of metallic cobalt is used to make the hardmetal cobalt with tungsten carbide, which was classified in Group 2A, with "limited" evidence in humans. Cobalt metal alone was classified in Group 2B, with "inadequate" evidence in humans. Mechanistic evidence, including of mutagenicity, was "strong" in experimental systems for cobalt with tungsten carbide but not for cobalt metal alone. Evidence of oxidative stress *in vitro* was weak for cobalt metal alone but was exacerbated for cobalt with tungsten carbide.

Research Recommendations included updating of the French and Swedish cohorts of hardmetal production workers [exposed primarily to cobalt with tungsten carbide (WC-Co)], pooling cohorts with other international studies, incorporating biomarkers

of exposure and mechanistic end points of early cellular effects (e.g., oxidative stress), and consideration of genetic polymorphisms.[6,7] No specific Research Recommendations were made for cobalt metal without tungsten carbide.

The 2019 Advisory Group recommended cobalt and cobalt compounds be reevaluated with high priority based on new mechanistic evidence, including the potential for cell death, DNA damage, inhibition of DNA repair upon release of cobalt ions within the body, including in exposed humans and human cells and tissues.[16,18] In 2022, metallic cobalt without tungsten carbide, and cobalt (II) compounds, were reevaluated for carcinogenicity.[29] WC-Co was not reevaluated. There was "strong" mechanistic evidence, including in human primary cells, that metallic cobalt is genotoxic and induces oxidative stress and that soluble cobalt compounds are genotoxic and induce cell proliferation, cell death, or nutrient supply. There was also "sufficient" evidence in experimental animals, and thus the classification was advanced to Group 2A.

The human cancer evidence for cobalt without tungsten carbide remained "inadequate." Studies (funded by the International Tungsten Industry Association) reported findings for lung cancer among hardmetal workers in Austria,[52] Germany,[53] Sweden,[54] the UK,[55] and the United States,[56] including in a pooled study.[57] Elevated lung cancer mortality rates were seen in comparison with national rates for short-term workers but, for long-term workers, they were seen only among women. There was no consistent evidence of positive exposure–response associations in the pooled cohort; individual country findings were heterogeneous. The pooled study did not incorporate biomonitoring for either exposure or mechanistic end points. The French cohort was not updated.[58] In a study of cancer incidence among nearly 1,000 cobalt production workers in Finland with follow-up for an average of 26 y, there was no association with lung cancer.[59]

Methylene chloride [dichloromethane (DCM)]. In 1998, DCM was classified in Group 2B.[30] Human cancer evidence was inconsistent, with small numbers of cancer cases, crude exposure characterization, and was, therefore, "inadequate."

Research Recommendations included new large cohorts, including female workers with robust current and retrospective exposure assessment and development of (urinary) biological markers.[6,7] Studies of film and textile workers, workers in furniture stripping, or automobile body repair shops were suggested. Cancer end points of interest included cancers of the brain, breast, and lymphohematopoietic system. Mechanistic research recommendations included studies of metabolism and metabolites of relevance for cancer at specific sites.

In 2014, DCM was classified in Group 2A, with "sufficient" evidence in experimental animals and "limited" evidence in humans for cancer of the biliary tract and non-Hodgkin lymphoma (NHL).[26] Among the epidemiological studies published since the Research Recommendations, there was an extended analysis of a cohort mortality study of workers in cellulose triacetate fiber and film facilities in England, with quantitative measures of DCM from area samples.[60] There were few cancer deaths and no clear findings according to categories of cumulative exposure. There were also other acetone and methanol exposures. There were some positive associations in population-based case–control studies, although numbers of exposed participants were small, and the participants were typically also exposed to other relevant solvents.[61,62] Findings for other cancers, including of glioma and meningioma risk, were "inadequate."[63,64] There was a small cluster of biliary tract cancer cases in Japanese printing workers exposed to DCM although workers were also exposed to other agents, including 1,2-dichloropropane (Group 1).[65] There was "strong" mechanistic evidence that DCM is metabolically activated to electrophiles via the glutathione *S*-transferase pathway and that DCM is genotoxic.

DCM was recommended for reevaluation by the 2019 Advisory Group with low priority.[16,18] There were new epidemiological studies, including of occupational and residential exposures for single cancer sites, including of the brain, breast, and lymphohematopoietic system, and there were additional studies of genotoxicity and oxidative stress.

PCBs. Early IARC WGs evaluated PCBs[66–68] and found that the human cancer evidence was mixed and involved several sites, first reaching "limited" for hepatobiliary cancer in 1987.[69] Analysis of human studies was complicated by the variety of PCB mixtures used in commerce and environmental and metabolic processes that alter the composition of PCB mixtures to which humans are exposed.[6,7,70]

Research Recommendations included new studies of highly exposed populations, including in a large U.S. National Institute for Occupational Safety and Health (NIOSH) cohort, as well as nested case–control studies in cohorts with blood levels of PCBs.[6,7] Mechanistic research needs included studies of reactive oxygen species (ROS), oxidative stress and DNA damage, formation of DNA adducts, and cell proliferation.

Epidemiological research strengthened the evidence for some cancer sites. In 2013, an IARC WG found "sufficient" evidence in humans for malignant melanoma and "limited" evidence for NHL and breast cancer.[25] All four previous evaluations had noted some evidence for malignant melanoma, and the latter two for lymphatic cancer. The most informative studies were those in industries where PCBs were used, including cohorts of workers in the manufacture of capacitors and transformers and in electric power and equipment maintenance, as well as population-based case–control studies with blood or adipose measurements of PCBs.

Studies published following the Research Recommendations workshop included a population-based case–control study of skin melanoma with lipid-adjusted plasma concentrations of 14 PCB congeners.[71] There were significant trends for dioxin-like and non-dioxin–like PCBs, as well as for 8 correlated chlorinated individual congeners. The association persisted after control for sun sensitivity and other potential confounders. New cohort studies included an updated follow-up of workers in capacitor production in Italy.[72] There was also a combined analysis in the U.S. NIOSH cohort of three capacitor-manufacturing facilities.[73] A significant positive association of semiquantitative job-exposure matrix-based cumulative exposure and breast cancer incidence was observed among non-White, but not White women. There were also nested case–control studies in general population cohorts with serum or adipose PCB concentrations with mixed or null findings. There were some positive associations of total serum PCBs and some PCB congeners and NHL risk in a nested case–control study in the Physicians Health Study.[74]

Regarding mechanistic data, the biologic effects of some PCB congeners are mediated through the aryl hydrocarbon receptor, through which 2,3,7,8-tetrachlordibenzo-para-dioxin (TCDD) causes cancer. In 2009, a WG convened as part of the IARC's Review of Human Carcinogens considered one dioxin-like PCB congener, 3,3′,4,4′,5-pentachlorobiphenyl (PCB-126), along with TCDD.[21] They classified PCB-126 in Group 1 based on "sufficient" evidence in experimental animals, "strong" evidence to support a mechanism mediated through the aryl hydrocarbon receptor, and extensive evidence showing activity identical to TCDD for every step of the mechanism of TCDD carcinogenesis in humans. Later, the 2013 WG used the same rationale to classify 12 dioxin-like PCB congeners in Group 1.[25]

The carcinogenicity of PCBs cannot be attributed solely to dioxin-like congeners and the aryl hydrocarbon receptor. The 2013 WG noted a complexity of relevant mechanisms, highlighting that PCBs are metabolized to electrophilic species, are genotoxic, induce oxidative stress, are immunosuppressive, induce chronic inflammation, and alter cell proliferation, cell death, and nutrient supply. The seminal paper on KCs cited PCBs as an example of an agent manifesting seven KCs of carcinogens.[10]

Styrene and styrene-7,8-oxide. In 2002, styrene was classified in Group 2B with "limited" evidence of carcinogenicity in humans and in experimental animals.[75] Although there were some positive findings in epidemiological studies for lymphatic and hematopoietic cancers, studies were small, and findings were often based on subgroup analysis. Styrene-7,8-oxide was classified in 1994 in Group 2A, based on "sufficient" evidence in experimental animals, "inadequate" evidence in humans (no data were available), and supportive mechanistic evidence that styrene-7,8-oxide forms covalent DNA adducts in humans and rodents and exhibits genotoxicity (both mutagenicity and cytogenetic effects) in human cells and experimental systems[76] (Table 2).

Research Recommendations included new cohorts of exposed workers and updating and pooling of glass fiber-reinforced plastics worker studies, including with improved exposure assessment and classification of lymphohematopoietic neoplasms.[6,7] Pooled studies on chromosomal aberrations and other genotoxic effects in exposed humans, extrahepatic metabolism of styrene, and formation of other genotoxic metabolites were suggested.

The 2014 Advisory Group recommended styrene for reevaluation with high priority.[15,17] The carcinogenicity of styrene and styrene-7,8-oxide was reevaluated in 2018.[28] Styrene was classified in Group 2A based on "sufficient" evidence in experimental animals, "limited" evidence in humans for lymphohematopoietic neoplasms, with supportive mechanistic data. The reevaluation included several updated cohorts with extended follow-up in the reinforced plastics industry.[77–80] The pooled European styrene cohort was reanalyzed, and outcome information was regrouped to the approximate modern World Health Organization classification.[81] There was a study of U.S. workers in the boatbuilding industry.[82] Several population-based case–control studies were also conducted.

The most consistent evidence was seen for styrene and leukemia and (to a lesser extent) lymphoma in the reinforced plastics industry, but chance, bias, or confounding could not be ruled out. Studies in the reinforced plastics industry had higher exposures and fewer potential confounders than of rubber or styrene monomer workers; however, these are often short-term workers, in part due to health-related dropouts, because styrene and fiberglass are irritants and healthy worker biases were, therefore, of concern. The Danish cohort and the pooled European cohort had substantial exposure durations and intensities, and used high-quality exposure assessment, although there was some missing exposure information for early years. All except one study were of cancer mortality, not incidence. Few new mechanistic studies in exposed humans were published and the recommendation for pooled mechanistic studies of genotoxicity was not advanced.

Owing to research gaps noted in the 2018 reevaluation, the pooled reinforced plastics workers study is being updated with improved exposure estimation and adding the U.S. cohort. The U.S. cohort has subsequently been reanalyzed with improved exposure assessment, finding an association between cumulative exposure and leukemia mortality.[83] Another recent study adjusting for healthy worker survivor bias using g-estimation reported significant styrene-associated time-to-death acceleration for lung cancer.[84] Styrene-7,8-oxide remained in Group 2A based on "sufficient" evidence in experimental animals and mechanistic evidence that styrene-7,8-oxide, an electrophile, forms DNA adducts in exposed workers and is genotoxic in human-relevant systems.[28]

Trichloroethylene. In 1995, TCE was classified in Group 2A.[85] There was "limited" evidence for cancer of the liver and biliary tract and NHL in humans owing to small numbers of cancer cases, low levels of exposure or crude exposure information, and concern regarding potential residual confounding by other personal or solvent exposures.

Research Recommendations included meta-analyses of high-quality studies, new occupational cohorts without multiple solvent exposures, and mechanistic studies to understand which TCE metabolites are most relevant for cancer at specific sites, as well as effects on cell-signaling pathways and epigenetic changes.[6,7] Incorporation of data on genetic polymorphisms in glutathione *S*-transferase and CYP2E1 were suggested.

TCE was reevaluated in 2012 in Group 1 with "sufficient" evidence for kidney cancer and "limited" evidence for liver cancer and NHL.[24] There was stronger and more consistent evidence from case–control studies of kidney cancer, including evidence of an exposure–response relation from two recent studies carried out in France and Eastern Europe with detailed exposure assessment and information on other personal or occupational factors.[86–88] The importance of the glutathione conjugation metabolic pathway for kidney cancer was also supported in analysis of glutathione *S*-transferase theta 1 (*GSTT1*) polymorphisms.[88] Some positive associations were observed in previous cohort studies of aircraft and aerospace or other relevant workers. A meta-analysis reported positive associations of TCE and kidney cancer risk with little evidence of heterogeneity.[89]

For liver cancer, findings were generally inconsistent in individual studies, and there was a lack of data on potential confounders, including alcohol consumption. For NHL, there was weaker and less consistent evidence from case–control compared with cohort studies, differences in outcome classification, and some evidence for publication bias.

There was "strong" mechanistic evidence that TCE is metabolically activated to electrophiles and is genotoxic. TCE is also immunosuppressive.

The 2019 Advisory Group concluded that there was insufficient new epidemiological evidence for classification of additional cancer sites and, as such, did not recommend reevaluation.[16,18]

Welding fumes. Welding fumes was evaluated in 1989 and classified in Group 2B based on "limited" evidence in humans for lung cancer and "inadequate" evidence in experimental animals.[90] There were positive findings in cohort studies for lung cancer, although there were no clear differences by type of welder. Results from 12 case–control studies showed positive findings, although there were small numbers of exposed cases and concerns regarding residual confounding and publication bias.

Research Recommendations included additional studies among welders and other metal-working occupations to evaluate different dimensions of exposure and the welding environment, also with improved smoking data.[6,7] Although the utility of biomarker measurements was noted, the practical limitations of carrying out measurements retrospectively was recognized. Other Research Recommendations included more focused examination of genotoxic and nongenotoxic end points in exposed welders and in experimental systems, as well as the relative contributions of different fume components to carcinogenicity.

In 2014, welding and welding fumes were recommended by the Advisory Group for reevaluation with high priority.[15,17] In 2017, welding fumes was reevaluated and classified in Group 1, with "sufficient" evidence in humans for lung cancer and "limited" evidence for kidney cancer.[27] The evidence for cancer in experimental animals was advanced to "limited". Many human

cancer studies were conducted since the previous evaluation, with nearly half the total number of case–control studies, but no cohort studies, published since the Research Recommendations workshop. The SYNERGY pooled case–control study, which controlled for tobacco smoking, was influential.[91] The WG found that case–control and cohort studies were consistent across occupational settings, time periods, and countries in showing an elevated risk of lung cancer. Confounding by smoking and asbestos exposure were unlikely to explain the findings. Positive lung cancer associations were found for both arc and gas welding (welders typically were exposed to both types), and associations with lung cancer were not restricted to stainless steel welders. Findings were summarized in a subsequent meta-analysis.[92] For kidney cancer, positive associations were less consistent, based on small numbers, and there were concerns regarding potential confounding.

There was "strong" mechanistic evidence, including from >20 panel studies in welders exposed to stainless steel and mild steel welding fumes, that welding fumes induce chronic inflammation and are immunosuppressive. Numerous *in vivo* studies in rodents also supported this finding, particularly for chronic inflammation. Mechanistic studies published after the Research Recommendations report contributed information on nongenotoxic end points, particularly related to specific components of the welding environment.

Agents That Were Reevaluated and for Which the Classification Was Not Updated

Table 2 and Figure S1 present a summary of agents that have been reevaluated or partially reevaluated by IARC WGs where the overall classification did not advance.[24,27,28,93] For one agent, night shift work, there was limited evidence in humans for a larger number of cancer sites upon re-evaluation.

Indium phosphide and other indium compounds. Indium phosphide was classified in Group 2A in 2003, an upgrade from 2B, based on extraordinarily high incidences of malignant neoplasms of lung (and increases in other tumors) in rats and mice occurring at extremely low exposure concentrations of short duration (22 wk, followed for 2 y).[51] There were no informative human studies.

Research Recommendations suggested studies of U.S. semiconductor workers may be uninformative owing to a lack of historical exposure data and potential coexposures.[6,7] Rather, new cohorts of workers in secondary indium refining industries were recommended, with higher indium and lower cadmium coexposures than in primary refiners, as was further investigation of pulmonary effects in workers in Asia. Studies of biomarkers of genetic damage in cells of exposed workers were recommended, as was investigation of potential mechanisms of carcinogenicity in experimental systems.

Indium phosphide has not been reevaluated. However, indium tin oxide (ITO) was recommended with high priority for reevaluation in 2014,[15,17] and in 2017 was classified in Group 2B.[27] No studies of cancer in humans were identified. There was "sufficient" evidence of cancer in experimental animals and "strong" evidence that ITO induces chronic inflammation in experimental systems. Findings in exposed humans were suggestive, but findings were too few for conclusive determinations to be made with respect to the KCs for chronic inflammation, genotoxicity, cell proliferation, and oxidative stress. Indium compounds were not considered by the 2019 Advisory Group.[16,18]

Shift work. Shift work that involves circadian rhythm disruption was evaluated in 2007 and classified in Group 2A with "limited" evidence in humans for the carcinogenicity of shift work that involves nightwork."[94] The most consistent evidence was for female breast cancer, although there were few studies (largely among nurses), as well as concerns regarding potential residual confounding and inconsistent and limited exposure assessment.

Research Recommendations included better definitions of shift work, studies of markers of circadian disruption in non-day workers, better descriptions of controls and their exposure to light at night, and investigation of the effect of variations in expression of circadian genes on cancer risk.[6,7] IARC convened a workshop in 2009 on how "shift work" should be assessed in future studies.[95]

Night shift work was recommended with high priority for reevaluation in 2014,[15,17] and in 2019 was classified again in Group 2A.[93] The term night shift work was selected to better describe exposure in human studies. Evidence for cancer in humans was "limited", with positive associations observed between night shift work and cancers of the breast, prostate, colon, and rectum. There were a large number of new epidemiological studies and the quality of exposure assessment methods was a key aspect of their informativeness. The WG noted improved exposure assessment methods, primarily in case–control studies, and the largest and highest-quality case–control studies were given greater prominence in the evaluation. Results were less consistent among cohort studies. The large majority of informative studies were published since the Research Recommendations workshop.

For breast cancer, 9 informative case–control studies and an additional large, pooled case–control study were reviewed. The pooled study found positive associations with ever night shift work and number of night shift hours per week, but not with duration or other metrics.[96] For premenopausal women, there were positive associations with most night shift metrics, particularly for more intense schedules and for current or recent exposures. For cohort-based designs, 3 of 11 studies assessing ever/never exposure found positive associations. Among the 13 case–cohort, cohort, or nested case–control studies that evaluated duration of night work, 6 found an increased risk with longer duration. Given the heterogeneity of findings, bias could not be excluded with reasonable confidence. For prostate cancer and cancer of the colon and rectum, there was evidence suggesting positive associations, but there were smaller numbers of studies and the findings remained limited.[97–99]

There was "strong" evidence in experimental systems that alteration in the light–dark schedule is immunosuppressive, induces chronic inflammation, and alters cell proliferation, cell death, or nutrient supply. In female night shift workers, there was suggestive evidence for effects on estrogen levels. In both humans and experimental animals, alteration of the light–dark schedule altered serum melatonin and the expression of circadian genes. However, results were inconsistent in the few studies linking serum melatonin to cancer risk. Potential misclassification of evening work as night work and potential inclusion of night workers as controls remained of concern. Only a few studies of variations in expression of circadian genes on cancer in shift workers had been conducted and no consistent evidence emerged.

Styrene-7,8-oxide. Styrene-7,8-oxide is not detailed here. See above (Styrene and styrene-7,8-oxide).

Tetrachloroethylene. In 1995, Tetrachloroethylene (perc) was classified in Group 2A.[85] There was "limited" evidence for esophageal cancer, NHL, and cervical cancer in humans. Epidemiological studies had small numbers of cancer cases and lacked data on potential confounders.

Research Recommendations included new studies in dry-cleaning workers using exhaled-breath measurements, pooling of U.S. cohorts, and new cohort studies outside of the United States and Europe. They also included evaluation of the genotoxic and oxidative potential of alternative metabolic pathways, understanding of metabolism and metabolism differences between species, and identification of sensitive subpopulations and relevant target organs.[6,7]

Perc was reevaluated in 2012 and classified again in Group 2A, with "limited" evidence for urinary bladder cancer in humans.[24] The reevaluation noted positive associations in several cohort and case–control studies; however, there was crude exposure assessment (employment in dry cleaning), small numbers of exposed cases, and the lack of an exposure–response relationship. Results from three case–control studies of occupational or environmental exposure were mixed. There were no clear findings for other cancer sites, and concerns remained regarding potential confounding by tobacco smoking or for kidney cancer by TCE (Group 1). Perc can form genotoxic metabolites, particularly in the kidney. Multiple mechanisms may contribute to carcinogenesis in the liver. For bladder cancer, there were no available mechanistic studies.

Subsequent to the 2012 evaluation, new studies, including an extended follow-up of a U.S. cohort of dry-cleaning workers,[100] reported positive exposure–response relationships of a solvent exposure index and both bladder and kidney cancer risk, as well as of high solvent exposure and lymphatic/hematopoietic malignancies. A U.S. population-based case–control study reported positive associations of high cumulative hours of exposure and kidney cancer risk, independent of TCE.[101] Medium cumulative job-exposure matrix-based Perc exposure was associated with bladder cancer incidence in a large-scale Nordic study.[102] Interindividual toxicokinetic and kidney toxicodynamic variability was assessed in the Collaborative Cross mouse population.[103] Perc (and dry cleaning using Perc) was considered a high priority for reevaluation by the 2019 Advisory Group, owing to the new human cancer evidence.[16,18]

Agents That Have Not Been Reevaluated

Agents that have not been reevaluated by IARC WGs are summarized in Table 3 and Figure S1.[51,76,104–107] A brief description of each agent in relation to the research recommendations is presented below.

Atrazine. Atrazine was classified in Group 3 in 1998.[104] The human evidence was "inadequate" and consisted of a combined analysis of two retrospective U.S. cohorts with a positive but imprecise increased risk of NHL mortality with definite or probable triazine herbicide exposure, although there were few deaths and a lack of adjustment for other pesticide exposures. There were positive associations of NHL in U.S. case–control studies, although findings could not be attributed to atrazine specifically. The relevance of the mechanism whereby atrazine caused mammary tumors in Sprague–Dawley rats (non–DNA-reactive hormonally mediated) for humans was not clear.

Research Recommendations included updated follow-up of existing cohorts including the U.S. Agricultural Health Study (AHS), as well as of analysis of studies of biomarkers among corn farmers and studies in exposed women.[6,7] Atrazine is an endocrine disrupting compound with both estrogenic and anti-estrogenic properties. Among subsequent studies, in an updated follow-up of pesticide applicators in the AHS with more than twice the number of incident cancer cases there was no clear association of lifetime use or intensity-weighted lifetime days of use and cancer risk at most sites.[108] Some significant positive associations with thyroid cancer were observed although there was no trend and findings were based on small numbers of cases. In a further extended analysis, there was a significant trend of intensity-weighted lifetime days of use (20-y lag) and renal cell carcinoma, which persisted with further adjustment for cyanazine and alachlor.[109] An algorithm for estimating nonoccupational exposure for spouses of farmers was developed to quantify exposures from take-home, agricultural drift, and residential use.[110] There was no association of drinking water atrazine and ovarian cancer incidence among postmenopausal women in the Iowa Women's Health Study adjusting for other water contaminants.[111] Analysis of repeated urine samples from 30 Iowa corn farmers and 10 controls revealed higher levels of atrazine mercapturate, a metabolite of atrazine among farmers; however, there was no association of atrazine mercapturate with oxidative markers (malondialdehyde, 8-hydroxy-2′-deoxyguanosine, 8-isoprostaglandin- $F_{2\alpha}$) overall, and limited evidence among samples with detectable metabolite levels.[112]

Research Recommendations also included further studies to characterize mechanistic pathways in humans, as well as of immune function. Findings from some new mechanistic studies in experimental systems regarding genotoxicity reported that atrazine damages the integrity of DNA and the stability of the cell genome, whereas others indicated genotoxicity is minimal. Mechanistic evidence for immune suppression and chronic inflammation was also reported.[113,114] Atrazine was considered a medium priority for reevaluation by both the 2014 and 2019 Advisory Groups.[15–18]

Carbon black. Carbon black was classified in Group 2B in 2006.[107] Although two of the three studies of carbon black production workers observed excess risk of lung cancer, findings from other studies were mixed. The few studies that assessed exposure–response data for lung cancer provided weak or inconclusive findings and human evidence was "inadequate". Mechanistic data, particularly for lung cancer in rats, included a sequence of events that started with impaired clearance and accumulation of particles in the lung, causing inflammation, cell injury, and production of ROS that eventually leads to mutations. High retained mass lung burdens and decreased lung clearance have been also observed in coal miners, which led to the conclusion that animal cancer data obtained under conditions of impaired lung clearance are relevant to humans. However, this evidence was not used for a mechanistic upgrade [see also Titanium dioxide (TiO_2), below]. Ultrafine and engineered nano-forms of carbon black particles were not reviewed.

Studies published since the evaluation included an extended follow-up of the UK mortality study using "lugged" analysis (by period since leaving employment),[115] an industry-supported reanalysis of the German cohort,[116] and a combined reanalysis of two previous case–control studies.[117] Altogether results were inconsistent, although there was some persuasive evidence from the UK cohort.

Research Recommendations included updating cohorts with data on particle size and surface area, as well as studies in additional carbon black facilities.[6,7] It was also suggested that the U.S. study of carbon black production workers should be reanalyzed. Few additional epidemiological studies have been published subsequently, although they include two additional industry-supported reanalyses of the German cohort of carbon black production workers, which did not observe increased risk for lugged analyses,[118,119] the U.S. cohort,[120] and a meta-analysis.[121]

Research Recommendations also included new studies to examine the relationship between occupational exposure to carbon black and validated biomarkers of oxidative stress as early biological responses, as well as microRNA and immune and inflammation processes relevant to particle-induced lung cancer mechanisms. These exposure–response relationships should be quantitatively compared in humans and rodents, and the role of particle size examined. Carbon black was nominated for reevaluation with low priority by the 2019 Advisory Group.[16,18]

Chloroform (trichloromethane). In 1998, chloroform (trichloromethane) was classified in Group 2B.[104] Although some weak positive associations of chlorinated drinking water consumption and cancers of the urinary bladder, colon, and rectum were observed, there was crude exposure assessment, lack of consideration of other chloroform sources, coexposure to other

correlated water impurities, and inconsistent findings by gender; therefore evidence in humans was "inadequate".

Research Recommendations included new case–control studies with detailed assessment of chloroform as well as of other disinfection by-products (DBPs) across different exposure routes (drinking water, swimming, bathing), new pooled studies, and studies in exposed workers (competitive swimmers, indoor pool workers, medical personnel).[6,7] In 2011 and 2012, some haloacetic acids, the next largest grouping of DBPs in drinking water following trihalomethanes (THMs), including dibromoacetic acid, bromochloroacetic acid, dichloroacetic acid, and trichloroacetic acid, were also classified in Group 2B.[22,24] More than 600 DBPs have been characterized, including a range of chemical classes.[122]

Among subsequent studies, a recent U.S. case–control study reported positive associations of average daily and cumulative intake of THMs and bladder cancer risk, and some weak evidence of an association of showering/bathing with higher brominated THMs.[123] There was no clear association of average total THM concentrations at the residence and incident pancreatic, kidney, or ovarian cancer risk in a U.S. cohort of postmenopausal women,[124–126] although positive associations of total THM, bromodichloromethane, and trichloroacetic acid concentrations and rectal cancer were observed.[127] There were no clear associations of average lifetime residential total or brominated THMs and colorectal cancer risk in a case–control study in Spain and Italy, and a significant inverse association with chloroform.[128] There were positive associations of residential chloroform and breast[129] and prostate cancer risk[130] in Spanish studies.

Chloroform was not considered by the 2019 Advisory Group, although haloacetic acids (and other DBPs) were considered a high priority for evaluation based on the new human cancer, bioassay, and mechanistic evidence.[16,18] Haloacetic acids exhibit multiple KCs of carcinogens; primarily, they are electrophilic or can be metabolically activated to electrophiles, are genotoxic, and induce oxidative stress.[131,132] A metabolome-wide association study reported various molecular changes following swimming in an indoor pool, although the contribution of DBPs to physical activity could not be disentangled.[133] Short-term exposure to DBPs in swimming pools showed genomics responses indicative of cancer risk.[134]

Lead and lead compounds. In 2004, inorganic lead compounds were classified in Group 2A with "limited" evidence for stomach cancer in humans.[106] There was a lack of quantitative dose–response data, and potential residual confounding by personal factors or habits was of concern. Less consistent findings were observed for cancer of the lung, kidney, and brain. Organic lead compounds were classified in Group 3. Organic lead compounds metabolize at least in part to ionic lead.

Research Recommendations included new cohorts or extended follow-up of existing cohorts with documented lead exposure, assessing the correlation of blood lead with cumulative bone lead, and examination of genetic susceptibility factors.[6,7] Subsequently, findings from combined analysis of cohorts of workers in the United States, Finland, and the UK revealed significant positive trends of maximum blood lead and lung, bladder, brain, and laryngeal cancer mortality.[135] In Finland and the UK, significant trends of maximum blood lead and incident brain cancer (malignant), Hodgkin's lymphoma, lung cancer, and rectal cancer were observed.[136] In an extended analysis of a U.S. male lead worker cohort, there were positive trends of maximum blood lead and brain, laryngeal, lung, and NHL cancer mortality.[137] Past maximum blood lead was correlated with current bone lead.[138] In the Shanghai Men's and Women's Health Study cohorts there were some positive associations of estimated cumulative lead fume and lead dust exposure and meningioma risk in women, as well as cancer of the kidney and brain overall.[139] There was an interaction of occupational lead and genetic variation in delta-aminolevulinic acid dehydratase, *ALAD*, for prostate but not renal cell carcinoma.[140,141] In general population cohorts, there was a positive association of erythrocyte lead and lymphoid[142] but not breast cancer incidence.[143]

Research Recommendations included studies of mechanisms. A range of genotoxic effects of inorganic lead were subsequently reported in exposed workers, in human cells *in vitro*, and in nonhuman mammals *in vivo* and in nonhuman mammalian systems *in vitro*.[144–147] Mutagenicity was shown in workers from two different factories engaged in the production of lead–acid batteries and glass chips.[146] Inorganic lead compounds were recommended for reevaluation by the 2019 Advisory Group with high priority due to new mechanistic evidence.[16,18]

Metallic cobalt (with tungsten carbide). Metallic cobalt (with tungsten carbide) is not detailed here. Please see above Metallic cobalt (with or without tungsten carbide).

Propylene oxide. Propylene oxide was classified in 1994 in Group 2B.[76] The evaluation included one nested case–control study in a U.S. industrial cohort with small numbers of male lymphatic and hematopoietic cancer deaths, with no clear findings. Although other cohorts were identified, they were not considered informative because workers were also exposed to ethylene oxide (Group 1) and evidence in humans was "inadequate".

A subsequent U.S. cohort study of propylene oxide manufacturing workers reported no clear association with total and site specific cancer mortality (including pancreatic and lymphopoietic and hematopoietic malignancies) with categories of duration of employment.[148] Propylene oxide forms hemoglobin and DNA adducts and sister chromatic exchanges in exposed workers.[149,150]

Research Recommendations included new occupational cohort studies, including of women.[6,7] Some recent U.S. cohort studies examined environmental exposure to propylene oxide in ambient air and breast cancer risk. In the California Teachers Cohort, some positive associations with incident invasive breast cancer risk were observed overall, as well as in pre/perimenopausal women.[151] In the Nurses' Health Study II there was no clear association with incident breast cancer risk overall, although there were some positive findings with estrogen receptor–positive (ER^+) disease.[152] There was no clear association with breast cancer incidence in the U.S. Sister Study.[153]

Mechanistic evidence of propylene exposure includes evidence of genotoxicity in human monocytes,[154] and genotoxicity and oxidative stress in a Chinese urban population.[155] Other recent studies examined propylene oxide metabolites in electronic cigarette users.[156–158] Propylene oxide was not considered by the 2014 or 2019 Advisory Groups.[15–18]

RCF. RCF was evaluated in 2001 and classified in Group 2B.[105] There was a U.S. cohort of workers who produced RCF that found no significant increase in lung cancer mortality, although there were few lung cancer deaths and few participants with adequate exposure latency. A U.S. case–control study of workers in a continuous glass filament plant reported some inverse associations for lung cancer, although there were small numbers of exposed cases and, overall, and the human evidence was "inadequate".

Research Recommendations included new cohorts and further follow-up of established cohorts, as well as investigation of the impact of fiber length.[6,7] In subsequent studies, in an extended follow-up of the U.S. cohort, there was no positive association with lung cancer mortality overall, or among those with greater cumulative fiber exposure.[159] There were some significant positive associations of leukemia mortality overall and urinary cancer mortality among those with greater cumulative fiber exposure, although findings were based on few deaths. There were no

positive associations for self-reported incident respiratory or urinary cancer. There were increased pleural but not interstitial changes among RCF-exposed workers based on radiographic data. In a further follow-up of the cohort, there was also no increase in lung cancer mortality, but an elevated risk of urinary cancer mortality was seen among those with greater cumulative fiber exposure, compared with the general population, based on few observed deaths; residual confounding by cigarette smoking is of concern.[160]

French population-based case–control studies reported no clear association with cancer of the lung or head and neck.[161,162] One study reported a stronger exposure–response relation for pleural mesothelioma among participants exposed to both RCF and asbestos compared with asbestos alone.[163] A study in Chinese workers reported adverse respiratory effects of RCF and altered lung damage and oxidative markers.[164]

Mechanistic evidence for lung damage linked to immune suppression and oxidative stress was reported in experimental animals.[165–167] Oxidative stress and chronic inflammation have been also reported in several *in vitro* studies in human cells.[168,169] RCF was not considered by the 2014 or 2019 Advisory Groups.[15–18]

TiO_2. TiO_2 was evaluated in 2006 and classified in Group 2B.[107] There were few epidemiological studies. The most informative was a multicountry study of TiO_2 production workers in Europe that found a slightly increased risk for lung cancer compared with the general population but no positive exposure–response in internal analyses, and, overall, the evidence in humans was "inadequate". As for carbon black, the body of evidence regarding the pathways and mechanisms was not strong enough to warrant a mechanistic upgrade. Data on ultrafine (nano-scale) TiO_2 particles were considered in the evaluation of mechanistic data. Exposure in informative epidemiological studies and cancer bioassays was inferred for general respirable-sized TiO_2. A subsequent analysis of two case–control studies from Montreal reported no association with lung cancer.[117]

Research Recommendations concentrated on new cohort studies, especially for workers producing or using nano-scale TiO_2.[6,7] The need for well-characterized exposures including information on particle size, crystal structure, and surface properties, as well as adequate follow-up time, was noted. Cohorts of workers exposed to ultrafine TiO_2, used in the cosmetics industry, with workers handling or mixing TiO_2 powders with other ingredients, probably have the highest exposure. It was noted that NIOSH was conducting exposure studies of TiO_2 users to identify possible new cohorts.

Subsequently, two publications expanded on the first U.S. industry-based cohort study on lung cancer by enlarging the cohort to three plants and extending follow-up,[170] then by restriction of the cohort to workers exposed to TiO_2.[171] The authors did not report any increased risk of lung cancer associated with exposure to TiO_2. A recent reanalysis of TiO_2 workers in Europe noted the presence of a healthy worker survivor effect, and in analysis using the parametric g-formula to address this bias, a positive relation between TiO_2 exposure and lung cancer mortality was observed.[172]

The 2019 Advisory Group recommended with medium priority nanomaterials (such as TiO_2 or nanosilica) for reevaluation.[16,18] They noted, however, that the published epidemiological studies of TiO_2 and lung cancer were not of nano-TiO_2.

Conclusions

Progress in research on suspected carcinogens has clarified understanding of the carcinogenicity of several of the 20 priority occupational agents. Following the Research Recommendations workshop, new evidence, concerning cancer in humans and mechanisms, has supported updated IARC Monograph evaluations or partial evaluations by IARC WGs for 13 agents.[20–29,93] Overall, 9 agents were accorded higher overall classifications by IARC WGs.[20,22–29] Of these, 5 agents were reclassified from either Group 2A or 2B into Group 1 (acetaldehyde associated with consumption of alcoholic beverages, DEE, PCBs, TCE, welding fumes),[20,23–25,27] 3 agents were reclassified from Group 2B to 2A (DCM, metallic cobalt without tungsten carbide, styrene),[26,28,29] and 1 agent, DEHP,[22] was reclassified from Group 3 to 2B. Many of the advancements to Group 1 derived from results of epidemiological studies that were in progress at the time of the workshop, including updates of cancer incidence and mortality follow-up in existing cohorts. In addition to higher overall classifications, updates of studies led to identification of additional cancer sites; although in a few cases, new and higher-quality studies did not confirm or strengthen evidence for associations detected in earlier studies (e.g., evidence for some cancer sites moved from "limited" to "inadequate" for Perc).[24]

There are agents where the classification did not advance following reevaluation by IARC WGs for various reasons, including inconsistent findings, crude exposure assessment, small numbers of exposed cases, lack of an exposure–response, and remaining concerns regarding potential confounding or sources of bias.[24,27,28,93] However, updated evaluations highlighted stronger evaluations of some cancer sites (e.g., night shift work[93]) or carcinogen mechanisms relevant to KCs (e.g., DEHP[22]). There were no agents where the overall classification declined.

Research Recommendations for specific agents often included epidemiological research in new study populations but also recognized challenges in doing so, including those due to low exposure levels, multiple exposures, or difficulties in identifying or accessing workers.[6,7] Thus, in addition to the identification of new epidemiological study populations, Research Recommendations also emphasized the importance of improved (quantitative) exposure assessment and use of biomarkers of exposure and intermediate outcomes, such as genotoxicity, immunomodulation, and accounting for relevant genetic polymorphisms. Additional recommendations included enhancing statistical power through extended follow-up of cohorts, pooling of studies, or meta-analysis, and addressing concerns regarding residual confounding due to other occupational or nonoccupational factors. Large-scale studies and cohort consortia have informed causality assessment for a range of agents or exposures.[173]

Notable research gaps remain for several priority agents that have not been reevaluated. Outstanding research needs identified in 2009 include new occupational cohort studies of propylene oxide (including of breast cancer in women) and new or updated follow-up of cohort studies of RCF.[6,7] For these two agents, the literature did not advance sufficiently to be reevaluated or considered by the 2014 or 2019 Advisory Groups.[15–18] Five agents that have not been reevaluated (atrazine, carbon black, chloroform (haloacetic acids and other DBPs), lead and lead compounds, TiO_2), all with "sufficient" evidence in experimental animals, were accorded priority in 2019 for reevaluation.[16,18] Some agents that were reevaluated in Group 2A since 2009 (DCM, Perc), were recommended in 2019 for an updated reevaluation, with differing levels of priority, based on new evidence from epidemiological studies (metallic cobalt was reevaluated in 2022).[16,18] Acetaldehyde (Group 1) was also accorded high priority for reevaluation in 2019 based on new mechanistic evidence.[16,18] Any reevaluation, per the 2019 Preamble, would incorporate refined considerations of study quality, including of exposure assessment methodology in epidemiological studies and studies of mechanistic end points.[8]

Because studies of KCs can support and strengthen conclusions based on studies of cancer in experimental animals, high-quality mechanistic studies in exposed human populations may address important data gaps.[9,10] For several agents [chloroform (haloacetic acids and other DBPs), cobalt and cobalt compounds, lead and lead compounds], mechanistic studies were highlighted by the 2019 Advisory Group as potentially influential for clarifying the carcinogenicity of these priority agents.[16,18] For other agents, high-quality mechanistic studies (or studies in experimental animals as appropriate) could be considered.[174,175] "Strong" evidence of KCs in exposed humans combined with "sufficient" evidence for cancer in experimental animals are classified in Group 1.[8]

Strong mechanistic evidence has been used increasingly since 1991 in overall evaluations, and none of these mechanistic upgrades has been reversed in future evaluations.[176] For 2,3,7,8-TCDD, the mechanistic upgrade to Group 1 was later confirmed by human cancer evidence. However, supposedly strong mechanistic evidence that has been used to refute the human relevance of "sufficient" evidence from cancer bioassays has been repeatedly reversed (e.g., DEHP,[22] melamine[174]).

For some agents (e.g., TiO_2, styrene), recent attempts to account for methodological sources of bias, such as the healthy worker survivor effect, have led to new positive findings of associations, potentially of relevance to resolve classification uncertainties.[84,172] In follow-up to recommendations of the Preamble Advisory Group, a recent IARC workshop was held on new methods of epidemiological bias assessment in cancer hazard identification for use in Monographs evaluations.[177]

Overall, new research findings and updated evaluations have advanced understanding of the carcinogenicity of occupational agents accorded priority in 2009.[6,7] It is difficult to attribute any specific advances to the recommendations made, especially for agents that were reevaluated a short time after the 2009 report. Participation of leading experts also likely resulted in overlap between ongoing and planned research and the priorities identified. There are often lag times for implementation of research recommendations. Nonetheless, for several agents, studies that incorporated larger sizes, pooling, or improved exposure assessment, as recommended in the 2009 workshop, were important for the IARC reclassifications. Furthermore, Research Recommendations foreshadowed the potential importance of conducting studies relevant to the KCs in exposed human populations and in primary human cells based on their importance to overall classification in the new IARC Preamble.[8] Research Recommendations have been cited in several subsequent studies of priority agents, including of welding fumes, lead, PCBs, solvents or other related agents,[64,91,139,178–182] or in publications of occupational epidemiology more broadly.[183,184] In addition to specific Research Recommendations, current agent classifications, recent Monograph evaluations, and Advisory Group recommendations for future Monograph evaluations[16,18] often stimulate further research to address data gaps and research needs (e.g., see Styrene and TiO_2, above). Recent efforts in Europe have sought to inform advances in research on various topics, including of occupation and health.[185]

Despite significant progress, evidence gaps remain for many agents of concern. Improvements in study design and end point measurement have the potential to advance understanding of cancer causation by these agents. It will be particularly important for future efforts to identify gaps and priorities for new research to apply existing mechanistic knowledge regarding each agent to identify the most important outcomes to study to revolve classification uncertainties. Based on the progress and lessons learned since the 2009 workshop, a future workshop on research gaps and needs for new priority occupational and environmental agents should be convened.

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